Regulation of Positron Emission Tomography (PET) Drugs & Current Good Manufacturing Practice (CGMP)

Ravindra K. Kasliwal, Ph.D.
Office of New Drug Quality Assessment (ONDQA)
Division – III, Branch VII
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration

Outline

- Background on PET drug CGMP regulations and implementation
- Useful references and resources
- New Drug Application (NDA) regulations, application formatting and changes to approved applications
- PET CGMP regulations (21 CFR 212)

PET CGMP Regulations

- FDA published final rule for CGMP for PET drugs **(**21 CFR part 212) in the Federal Register of December 9, 2009 (74 FR 65409).
- Concurrently, FDA also announced the availability of a guidance entitled ‘‘PET Drugs—Current Good Manufacturing Practice (CGMP)” to help PET drug producers better understand FDA’s thinking regarding compliance with the new PET CGMP requirements.

PET Drugs Regulatory Framework

- PET CGMP regulations are effective as of December 12, 2011.
  - PET drug production is to be in compliance with 21 CFR part 212 (or other applicable provisions) from this date.
- In December 2012 FDA announced exercise of enforcement discretion until June 12, 2012.
- No enforcement discretion after June 12, 2012.
- Starting on this date, FDA will require the submission of a new drug application (NDA) or an abbreviated new drug application (ANDA) for a PET drug product in clinical use (as opposed to research or investigational) in the United States.
- PET producers must be operating under an approved NDA or ANDA, or an effective IND, by December 12, 2015.

Registration and Listing

- All PET drug producers must register and list under 21 CFR 207
  - Submit drug establishment and drug listing information through electronic submissions
  - Website for information

    http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/DrugRegistrationandListing/default.htm

Exceptions

- Provisions of USP Chapter* <823> will apply when PET drugs are produced under,
  - Investigational New Drug Application (IND)
  - Radioactive Drug Research Committee (RDRC)
  - Have option to follow the requirements in 21 CFR 212
- IND and RDRC holders are not required to register and list PET drugs

*USP Chapter <823> ‘‘Radiopharmaceuticals for Positron Emission Tomography— Compounding,’’ (USP 32/NF 27) (2009)

Resources for PET Drugs

Visit FDA PET Web Page:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm

- Federal Register Notice: Final Rule- CGMP For PET Drugs
- PET Drug Products – CGMP Guidance
- PET – Questions and Answers About CGMP Regulation of PET Drugs
- PET Additional Questions and Answers Based on December 9, 2009 Stakeholder call
- Media Fills For Validation of Aseptic Preparations For Positron Emission Tomography - Guidance
- CPGM: PET CGMP Drug Process and Pre-approval Inspections/Investigations
- FAQ Guidance

Can a PET drug be produced and distributed after June 12, 2012?

- If you were using a PET drug for clinical use before June 12, 2012,
  - You can continue to produce and use the PET drug if an application for the drug has been submitted by June 12, 2012, and is under review at FDA
    - Fludeoxyglucose F 18 injection, Sodium Fluoride F 18 injection and Ammonia N 13 injection
  - Many scenarios regarding production and use are discussed in “Guidance - FDA Oversight of PET Drug Products - Questions and Answers”

Useful Questions and Answers

- Guidance - FDA Oversight of PET Drug Products - Questions and Answers
  - Help producers of positron emission tomography (PET) drugs meet the requirements for FDA's drug approval process.
    - Application submission and review
    - Compliance with current good manufacturing practices
    - Inspections
    - Registration and listing
    - User fees.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM290024.pdf

Regulations for Applications

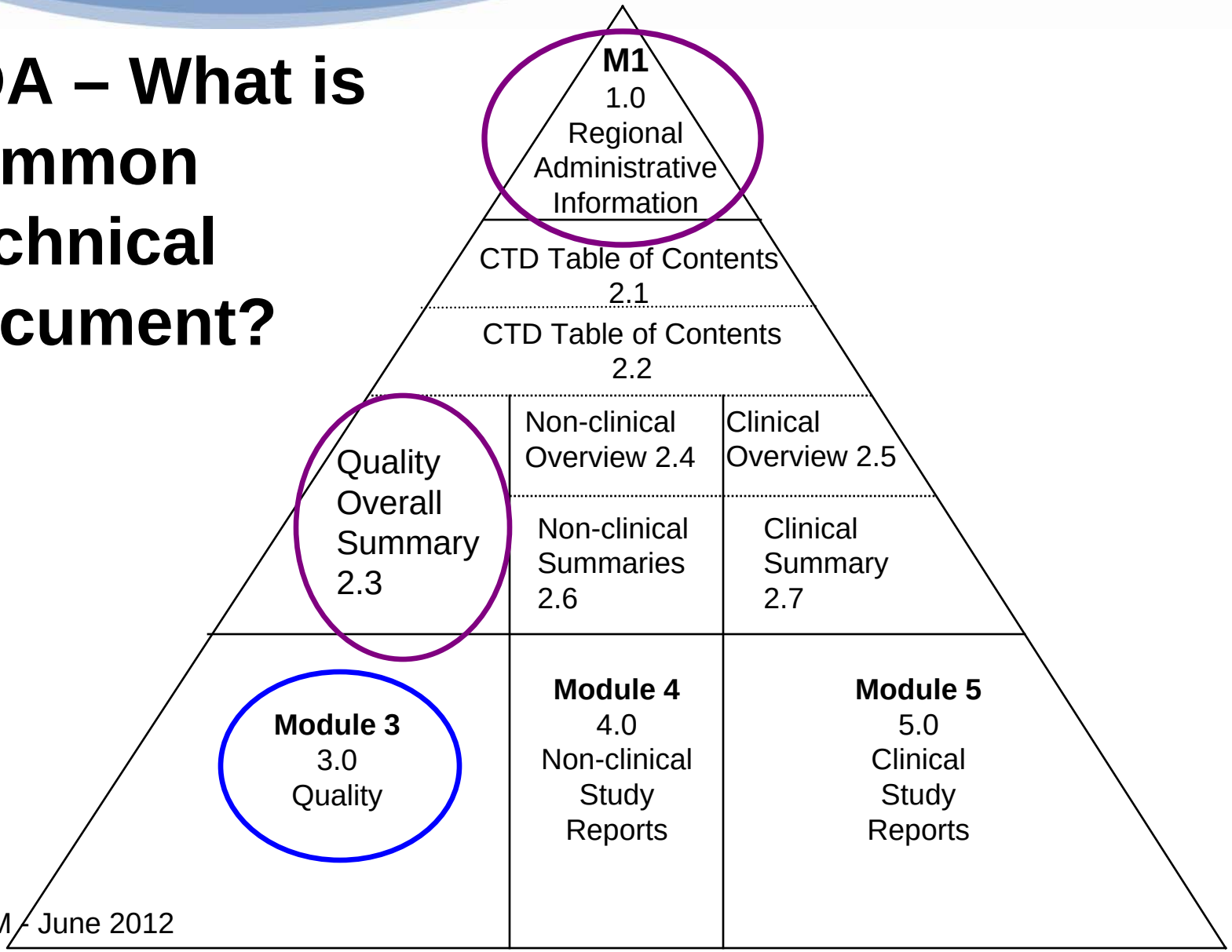
- NDA Regulations
  - 21 CFR 314 – Application for FDA approval to market a new drug
  - 21CFR 314.50 – Content and format of an NDA
  - 21CFR 314.50(d)(1) – Chemistry, Manufacturing, and Controls section
- ANDA Regulations
  - 21 CFR 314 (Subpart C)
    - 21 CFR 314.92 – 21 CFR 314.99

Chemistry, Manufacturing and Controls (CMC) in NDAs

- Current preferred format for submitting an application, including CMC, is the Common Technical Document (CTD)
  - Paper CTD or
  - electronic CTD (e-CTD) format
- Guidance:
  - Submitting Marketing Applications According to the ICH-CTD Format —General Considerations
  - M4Q: The CTD — Quality; M4: The CTD — Quality Questions and Answers/ Location Issues
  - website:

    http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065006.htm

NDA – What is Common Technical Document?



Drug Substance in NDA - CTD

- **S.1 General Information: Nomenclature, Structure, General Properties**
- **S.2 Manufacture**
  - **Manufacturers**
  - **Description of Manufacturing Process and Process Controls**
    - **Flow diagram**
    - **Process Narrative**
    - **Process Controls**
  - **Control of Materials**
    - **Starting Materials**
    - **Reagents, Solvents, Auxiliary Materials**
  - **Control of Critical Steps and Intermediates**
  - **Manufacturing Process Development**
- **S.3 Characterization**
  - **Elucidation of Structure**
  - **Other Characteristics**
    - **Physicochemical properties**
    - **Solid State Forms**
  - **Impurities**
    - **Types (organic, inorganic, residual solvents)**
    - **Classification (specified/unspecified, identified/unidentified)**
    - **Reporting, Identification and Qualification Thresholds**
    - **Acceptance Criteria**
    - **Qualification**
- **S.4 Control of the Drug Substance**
  - **Specifications**
  - **Analytical Procedures**
  - **Validation of Analytical Procedures**
  - **Batch Analyses**
  - **Justification for Specifications**
- **S.5 Reference Standards**
- **S.6 Container Closure System**
- **S.7 Stability**
  - **Stability Protocol and Data Evaluation**
  - **Forced Degradation/Stress Testing**
  - **Photostability**
  - **Stability Summary and Conclusion**
  - **Post-approval Stability Protocol and Commitment**
  - **Stability Data**

Drug Product in NDA - CTD

- **Drug Product**
- **P.1 Description and Composition**
- **P.2 Pharmaceutical Development**
  - **Drug Substance**
  - **Excipients**
  - **Formulation Development**
  - **Manufacturing Process Development**
  - **Container Closure Suitability**
- **P.3 Manufacture**
  - **Manufacturer**
  - **Batch Formula**
  - **Description of Manufacturing Process and Process Controls**
  - **Control of Critical Steps and Intermediates**
- **P.4 Control of Excipients**
- **P.5 Control of the Drug Product**
  - **Specifications (release, stability, in-house)**
  - **Analytical Procedures**
  - **Validation of Analytical Procedures**
  - **Batch Analyses**
  - **Justification of Specifications**
- **P.6 Reference Standards**
- **P.8 Stability**
- **P.7 Container Closure Systems**
  - **Primary, Secondary, Functional and Non-Functional Secondary Packaging**
  - **Stability Protocol and Data Evaluation**
  - **Forced Degradation/Stress Testing**
  - **Photostability**
  - **Stability Summary and Conclusion**
  - **Post-approval Stability Protocol and Commitment**
  - **Stability Data**
- **Regional Information**
- **Executed Batch Records**
- **Comparability Protocols**
- **Method Validation Package**
- **Module 2 of CTD**
  - **Quality Overall Summary**

Drug Master Files

- A DMF contains information about a drug substance, a component, or a container/closure system that is proprietary (i.e., belongs to someone else)
  - Type II - Drug substance, drug substance intermediate, and materials used in their preparation, or drug product
  - Type III - Packaging materials
  - Type IV - Excipient, colorant, flavor, essence, or materials used in their preparation
  - Type V - FDA accepted reference information

Drug Master Files

- The information may not be available to you, but you may need it as part of your NDA, ANDA
- The CMC section may ask you to provide this information
- This information is usually available from the supplier or manufacturer of the subject of the DMF
- Rather than providing the information directly to you, the manufacturer may choose to *hold a DMF*. The DMF holder provides the information directly to the FDA (submits DMF to FDA)

DMF Reference

- If a manufacturer holds a DMF that you would like to reference, you should ask them to provide you with a letter of authorization (LOA), which you must include with (and reference in) your application and list on your Form 356h
- LOA from the DMF holder grants the FDA authorization to refer to information in their DMF during the review of your NDA, ANDA or IND

Drug Master Files (DMF) Resources

- The regulatory requirements for a DMF-21 CFR 314.420
- Guidance:
  - Guideline for Drug Master Files
    - http://www.fda.gov/cder/guidance/dmf.htm
- Current DMF submission address:

  Food and Drug Administration
  Center for Drug Evaluation and Research
  Central Document Room
  5901-B Ammendale Road
  Beltsville MD 20705-1266

Changes to Approved NDA / ANDA

- The applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application.
- The holder of an approved application under section 505 of the act must assess the effects of the change before distributing a drug product made with a manufacturing change.

Changes to Approved NDA / ANDA

- 21 CFR 314.70 – type of changes and how to report them.
- Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes): *Prior Approval Supplement*
- Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes): *Supplement-Changes Being Effected in 30 Days.*
- Changes requiring submission of an supplement where applicant may commence distribution of the drug product involved upon receipt by the agency of such supplement: *Supplement-Changes Being Effected.*
- Changes to be described in an annual report (minor changes)

What are CGMPs for PET drugs?

Current good manufacturing practices for PET drug products are the minimum requirements for the methods to be used in, and the facilities and controls used for, the production, quality control, holding, or distribution of a safe and effective PET drug product intended for human use.

Elements in PET Drug CGMP

1. Personnel and Resources **[212.10]**
2. Quality Assurance **[212.20]**
3. Facilities and Equipment **[212.30]**
4. Control of Components, Containers, and Closures **[212.40]**
5. Production and Process Controls **[212.50]**

Elements of PET Drug CGMP, continued

6. Laboratory Controls **[212.60]**
7. Drug Product Controls and Acceptance criteria **[212.70]**
8. Packaging and Labeling controls **[212.80]**
9. Distribution controls **[212.90]**
10. Complaint Handling **[212.100]**
11. Record keeping **[212.110]**

CGMP Systems

1. Quality system with aseptic sterility controls
2. Facilities and Equipment system
3. Materials system
4. Production system
5. Packaging and Labeling system
6. Laboratory Control system

CGMP Systems

- Compliance Program Guidance Manual – 7356.002P
  - POSITRON EMISSION TOMOGRAPHY (PET) CGMP DRUG PROCESS AND PRE-APPROVAL INSPECTIONS / INVESTIGATIONS
- Webinar on CGMP for PET Drugs
- Links are provided on FDA / CDER PET Drug page:

  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm

Personnel and Resources – [212.10]

- Sufficient number of qualified and trained personnel to perform their assigned tasks.
  - Facilities where few individuals are employed, one individual can be assigned to perform both production and quality assurance tasks.
- Sufficient resources including equipment, facilities and personnel to produce a quality PET drug.

Quality Assurance – [212.20]

- Person or organizational element responsible for the duties relating to quality control.
- Oversees production operations to ensure that a quality PET drug is produced.
- Examines and approves or rejects components, containers, closures and the finished PET drug.
- Approves or rejects procedures and/or specifications

Quality Assurance, continued

- Reviews production records for accuracy & completeness.
- Ensures that investigations have been conducted and corrective action taken.
- Approves change control.
- Oversees complaints, adverse reactions.
- It's possible for a certain part of the QA function to be at a centralized off-site location, however, batch release must be signed off on-site by a responsible QA individual

Facilities and Equipment – [212.30]

- Equipment: clean, suitable for its intended purposes, properly installed and maintained.
- Facilities: adequate to assure the orderly handling of materials and equipment, prevent mix-ups and contamination of equipment and the PET drug.

Control of Components, Containers, and Closures – [212.40]

- Procedures for the handling of components.
- Establish appropriate specifications, and examine each lot upon receipt with established specifications.
- Each lot must meet all established specifications to be used in production.
- Instead of full testing, a certificate of analysis (COA) may be accepted provided the PET center establishes the reliability of test results.
- Use qualified vendors.
- Centralized acceptance of components, container and closures is possible.

Recycling of $H_2{}^{18}O$

- Establish procedure for the recycling, reprocessing and specification of the reprocessed $H_2{}^{18}O$
- Use $H_2{}^{18}O$ of acceptable quality

Production & Process Controls - [212.50]

- Ensure consistent and quality production
- Establish written procedures, master and batch production and control records.
- Include inspection of the production area and all equipment for suitability and cleanliness before use.
- Process verification results must be documented

Production & Process Controls, cont.

- Prepare batch production and control record for each batch of PET drug produced.
- Batch record should include the critical production steps and test results
- Deviations from established procedures must be investigated and documented
- The process must be validated.

Packaging & Labeling Controls – [212.80]

- Packaging and shipping containers should protect against damage during storage, handling, distribution, and use.
- Use approved (NDA or ANDA) packaging and labeling.
- Label information should conform to 21CFR 201.
- Operations should be controlled to prevent mix-ups.
- Labels must be legible.

Laboratory Controls – [212.60]

- Follow written procedures and document each laboratory test results.
- Analytical methods should be suitable, sensitive, specific, accurate, and reproducible.
- Control the identity, purity and quality of reagents, solutions and supplies used in testing procedures.
- All testing equipment must be suitable for its intended purpose and capable of producing valid results.

Laboratory Controls, cont.

- Test records
  - a complete description of the sample received
  - a reference to the method used
  - raw data: including charts, graphs and calculations
  - results: pass or fail acceptance criteria
  - initials or signature of the person performing the test
- Program to assess the stability of a PET drug, including suitable storage conditions, use of reliable and specific test methods, and expiration dates/ times

Stability Studies

- The drug product should be assessed for stability - both radiolysis and chemical degradation (e.g. pH dependant).
- Where there is to be a range of radioactivity, stability should be assessed at the upper limit.
  - 3 Batches (each for different formulations and synthesizers)
- Stability studies should be performed in the container closure in which the drug product will be stored.

Drug Product Controls and Acceptance Criteria – [212.70]

- Establish procedures for release:
  - complete laboratory testing and review data
  - release authorized by designated person
- Each batch must meet its established acceptance criteria prior to release.
  - If product does not meet acceptance criteria: reject product; conduct investigation and take action to correct any identified problems.

Analytical Procedure Information in Drug Applications

- For Analytical Procedures
  - The analytical supplies and their quality used
  - The equipment and the settings used during the performance of the procedure
  - The preparation of test, standard, and analytical solutions
  - The system suitability test(s) performed (including system suitability standards used, and the acceptance criteria that ensure proper performance of the equipment)
  - Detailed description of the test procedure
  - Exact calculations performed in quantitative procedures
  - The recording of the results
  - Validation data

Sterility Testing - 21CFR 212.70(e)

- Testing required within 30 hours
- Extension allowed (validation needed)
- Testing samples (individual, not pooled)
- Report sterility failure
- Document sterility failure
- Conduct investigation
- Notify receiving facilities

Bacterial Endotoxin Testing

- Product conforms to endotoxin specification BEFORE final release
- Reference USP <85> or method established in drug application
- Methods
  - Materials
  - Controls
  - Suitability test

Conditional Release – [212.70(f)]

- Conditional release is permitted, if one finished product test[1] cannot be completed due to an analytical equipment malfunction, when the following conditions are met:
  - Prior history demonstrates that the final release of the product will meet the established specifications.
  - The malfunctioning analytical equipment is immediately fixed or replaced.
  - Product identity, purity, and specific activity are verified.
  - No additional batches of product are released until the problem is corrected and the omitted finished product test is reinstated.

[1]All other finished product acceptance criteria must be met. Document all actions that justify the conditional release of product.

Distribution Controls – [212.90]

- Drug products should be shipped in accordance with labeling conditions.
- Establish and follow procedures if the drug is distributed or shipped.
- Keep adequate distribution records
  - The chain of distribution of each batch of drug product must be readily determined to permit its recall if necessary.

Record Keeping – [212.110]

- Maintain records at location that is reasonably accessible.
- Keep records for 1 year from the date of drug product release.
- Records to include:
  - Composition and quality,
  - Production operations, batch records, and out-of-specification results
  - Distribution and complaints.
- Records: legible and readily available for review and copying by FDA.

Complaint Handling – [212.100]

- Establish procedures to handle complaints pertaining to the quality and labeling, or possible adverse reactions.
  - A written record of each complaint, the investigational findings, and follow-up must be maintained.
  - A drug returned due to a complaint must be destroyed.
  - Corrective action should be taken immediately if there is reason to believe that an adulterated drug was implicated in the complaint.
- Written complaint records must include:
  - drug name, strength
  - batch number
  - date and nature of complaint
  - response to complaint
  - findings of investigation, follow-up

Conclusion

- Backgroung on PET drug CGMP regulations and implementation
- Useful references and resouces
- NDA application regulations, application formatting and changes to an approved application
- PET CGMP regulations (21 CFR 212)

Thank-you